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EXAMINER	
SINGH, ANOOP KUMAR	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/658,688	HERMANSON, GARY G.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *215-292* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *215-292* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on September 11, 2006 has been received and entered. Claims 1-214 have been canceled, while applicants have added claims 215-292.

Election/Restrictions

Applicant's election with traverse of the invention of claims 174 and 214 (group II) filed January 30, 2006 was acknowledged. The traversal was on the grounds(s) that Examiner did not set forth convincing argument that the search and examination of group I along with elected group necessarily represents an undue burden for the examiner. Applicants' argument of examining plurality of polynucleotide composition with the elected group comprising a method of treating anthrax was found not persuasive. Applicant's argument of examining other sequences with elected Seq ID 4 was found not persuasive. Examiner also indicated that fragments and variants of SEQ ID NO: 4 such as SEQ ID 2, 6 and 8 would be examined as long as they depend on elected claims.

Claims 215-292 are under consideration.

Information Disclosure Statement

The submission of information disclosure statement (IDS) filed on 9/11/2006 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

Withdrawn-Claim Objections

Claim 174 objected to because it continued to depend in part to withdrawn claim is withdrawn in view of cancellation of claim 174.

New-Specification

The disclosure is objected to because of the following informalities: The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See page 23, paragraph 67, line 5, page 36, line 1). The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor error. Applicant's cooperation is requested in correcting errors of which applicant may become aware in the specification. Appropriate correction is required.

New-Claim Rejections-Necessitated by the Amendments - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 215-292 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method to reduce the severity of anthrax infection in a mammal comprising: administering to a mammal a composition comprising a carrier, (+)-N- (3-aminopropyl)-N,N-dimethyl-2,3-bis(syn-9-tetradecenyloxy)-l-propanaminium bromide (GAP-DMORIE), a co-lipid selected from the list consisting of 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), 1,2-diphytanoyl-sn-glycero-3-phosphoethanolamine (DPyPE), and 1,2-dimyristoyl-glycer-3-phosphoethanolamine(DMPE) and an isolated polynucleotide comprising a nucleic acid fragment which encodes a polypeptide at least 97% identical to amino acids 199 to 764 of SEQ ID NO:4, wherein said nucleic acid is ligated to a heterologous nucleic acid; wherein said heterologous nucleic acid encodes a heterologous polypeptide comprising human tissue plasminogen activator (hTPA) signal peptide fused to the polypeptide encoded by said nucleic acid fragment;

wherein said composition elicits an immune response to said polypeptide; and wherein said nucleic acid fragment is a variant fragment of an optimized coding region for the polypeptide of SEQ ID NO: as set forth in claim 215; does not reasonably provide enablement for a method of preventing anthrax or eliciting immune response infection to treat anthrax infection . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

The office has analyzed the specification in direct accordance to the factors outlines in *In re Wands*. MPEP 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on factors discussed in MPEP 2164.01(a) and the evidence as whole, it is not necessary to discuss each factor in written enablement rejection." These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

Claims 215 and 245 are drawn to a method to prevent anthrax infection in a vertebrate comprising administering to a vertebrate in need thereof a composition comprising a carrier and a nucleic acid fragment that encodes a polypeptide at least 97% identical to amino acid 199-764 or 30 to 764 of SEQ ID NO: 4 which are variants of an optimized coding region for the polypeptide of SEQ ID NO:4 and for eliciting an immune response to said polypeptide. In addition, it is noted that claims 231and 261 are

directed to a method of treating anthrax infection by delivering the composition of the invention. It is emphasized although claims 275-292 are drawn to a composition and carrier, however they are also analyzed for their intended use in method of treating or preventing anthrax infection as contemplated in the instant invention.

The aspects considered broad are: methods of treating or preventing anthrax infection of by merely eliciting immune response to the composition of the invention at any level in any subject. It is noted that as recited, claimed invention reads on broad genera of DNA vaccine by delivering codon-optimized polynucleotide to elicit immune response. The specification fails to provide an enabling disclosure for the claimed invention because the specification fails to provide sufficient guidance as to (i) how an artisan of skill would have practiced the claimed method in treating or preventing any form of anthrax infection by administering via any route and expressing plurality of codon optimized polynucleotide, (ii) the claimed method would have resulted in immune response sufficient to treat or prevent any form of anthrax. An artisan would have to carry out extensive experimentation to make and use the invention, and such experimentation would have been undue because art of gene delivery *in vivo* is unpredictable and specification fails to provide specific guidance to practice the invention over full scope. As will be shown below, these broad aspects were not enabled for the claimed invention at the time of filing of this application because neither the specification nor the art of record taught sufficient guidance to practice the invention over full scope of the claims. For purposes to be shown in the state of the prior art, the question of lack of enablement is discussed.

The specification provides a general description of anthrax infection and describes the role of toxins consisting of gene product protective antigen, lethal factor, and edema factor in the virulence of *Bacillus anthracia* infection (pp 1-2). The specification also describe the need for optimization of coding regions encoding polypeptides from pathogen codon frequencies preferred in a mammalian species resulting in enhanced expression in the cells of that mammalian species and concomitant increase in immunogenicity (pp 5). The invention is directed to enhance immune response of a vertebrate that require protection against anthrax by

administering in vivo a polynucleotide comprising a codon optimized coding region encoding a component of *Bacillus anthracia* lethal toxin (pp 5-6). Pages 7-11 describe brief description of the drawing. Pages 11-67 of the specification provides a detailed description of the invention, preferred embodiments and provide definition of terms, codon optimization (pp 21-54), methods and administration of claimed compositions of the invention (pp 54). Rest of the specification provides specific examples of plasmid vectors, compositions and experimental details (pp 68-120).

As a first issue, the claim 215 embrace an isolated polynucleotide comprising a nucleic acid fragment which encodes a polynucleotide at least 97% identical to amino acid 199-764 or 30 to 764 of SEQ ID NO: 4, wherein said nucleic acid fragment is a variant fragment of an optimized coding region for the polypeptide of SEQ ID NO: 4. The specification discloses a nucleic acid region for full length protective antigen (PA) (SEQ ID NO:4) and asserts other sequences that are human codon optimized coding region that encodes SEQ ID NO 4 (pp 71, para. 157). The specification also teaches PA sequence encodes a 764 amino acid precursor protein that is processed by a signal peptidase upon secretion by the bacteria. However, specification fails to provide an enabling disclosure for the full scope of the claimed nucleic acid sequence. It is not apparent from the specification whether any sequence with 97% identity to SEQ ID 4 that is optimized for human codon would elicit effective immune response against *Bacillus anthracia* infection. The specification fails to provide adequate guidance how to make and use altered nucleic acid sequence for nucleic acid sequence ~97% identical to SEQ ID NO: 4, wherein fragment is a variant fragment of an optimized coding region for the polypeptide of SEQ ID NO 4. Nagata et al (Biochem Biophys Res Commun. 1999; 261(2): 445-51) state, "inter specific difference of codon usage is one of the major obstacles for effective induction of specific immune responses against bacteria by DNA immunization". Nagata et al show that DNA immunization using the gene codon-optimized to mammals through the entire region is very effective (abstract). However, it is noted that Nagata et al suggest that translational efficiency of codon-substituted gene in mammalian cells does correlate but is not proportional to codon adaptation index (CAI) values of the genes in the mammals (Figure 2). Nagata et al conclude that only

optimal codon usage elicit effective immune response (Figure 3 and pp 450, col. 2, last para). Thus, it is apparent that an artisan would have to carry out extensive experimentation to make and use the invention, and such experimentation would require undue experimentation to practice method as claimed because only optimal codon usage in mammals would have provided optimal immune response sufficient for the treatment of *Bacillus anthracia infection*

While the specification provides a description of DNA vaccine for the protection against anthrax, the specification does not teach specific information required by the artisan to reasonably predict that any form of anthrax infection can be treated or prevented by administering codon optimized DNA vaccine via any route such that it elicit an immune response that is effective for long enough for sustained period of time that would have beneficial effects in preventing or treating anthrax infection.

Applicant does not enable administering DNA vaccine via any route using any carrier to elicit an immune response. While progress has been made in recent years in development of DNA vaccine against viral as well as bacterial infection, however, desired immune response for sustained period continued to be unpredictable and inefficient in humans.

The state of the post filing art effectively summarized by the references of Galloway et al (Expert Opin Biol Ther. 2004, 4(10): 1661-7) describe progress made in DNA vaccine for the treatment and prevention against anthrax infection. Galloway state, " a number of factors may account for poor immunogenicity of plasmid DNA in non human primate and human. Of the prime importance is the issue of DNA uptake and antigen presentation" (pp 1665, col. 1, last para). It is disclosed that codon usage and cationic lipids improve the efficacy of the antigen presentation and resulting immune response. However, Galloway concludes, " the field of DNA vaccination remains largely an experimental and some what empirical science" (pp 1665, col. 2, para. 4, lines 1-4). They highlight some advantages of using DNA vaccine but also acknowledge the fact the no DNA vaccine is yet produced is not the research failure but rather realization of complex role of immune system (pp 1665, col. 2, para. 4). The prior art of record on treating anthrax by recombinant anthrax vaccine was unpredictable as a

number of question remain unanswered that require experiment that are not routine to determine whether the vaccine would be efficacious in any patient. For instance, Leppla et al (J Clin Invest. 2002,110(2): 141-4) while reviewing state of anthrax vaccine raise a number of questions. Leppla et al describe that limited clinical data and substantial animal experimentation indicate that only a critical level of serum anti-PA antibodies confer immunity to both cutaneous and inhalation anthrax. Leppla further describe a number of other uncertainties including what would be the optimal concentration of serum antibodies in humans that confers immunity to anthrax. Thus, a regimen of dose scheduling as disclosed from small animal and primate would not be efficacious to confer immunity in humans. In addition, the level of antibody required to protect individual from the effects of a anthrax infection is uncertain, since this would be dependent upon how the infection is acquired (bio-terrorist attack, natural, Zoonotic) and the number of spores inhaled. Similarly, the efficacy of this DNA vaccine would also be different depending upon source and route of anthrax infection (inhalation, cutaneous). The working example shows immune response against spore challenge of $50LD_{50}$- $250LD_{50}$. It is not apparent whether it would confer protection against anthrax infection of 500- 5000 LD_{50}. Leppla also questioned whether physicochemical and immunochemical assays could accurately predict the efficacy of a recombinant vaccine (pp 143, col. 2, para 2 bridging pp 144, col. 1, para. 1). The specification does not provide any specific guidance to overcome this art recognized limitations of dose, type and route of anthrax infection and levels of antibody optimal for protection or treatment in any subject (emphasis added).

Given this lack of reasonable predictability in Applicant's specification and the art, the Artisan would require a large amount of information from Applicant's examples to provide the guidance to provide reasonable predictability.

Applicant's examples describe the construction of an isolated polynucleotide comprising a human codon optimized PA, LF, fragments and variants thereof encoding full length *B. Anthracis* protective antigen (PA), LF and variant. The results show *in vitro* expression of human codon optimized coding regions encoding *B. Anthracis* PA, LF and fragments in a murine and human cell lines. The samples were assayed for by western

blot and ELISA using anti PA, anti LF antibodies (pp 88-89). Examples 8 and discloses mouse, rabbit, non-human primate and human immunization by administering plasmid constructs intramuscularly and immunological assay to determine LF and PA antibody titer (pp 93-95). Examples 11-12 describe immunization of mice and rabbit using codon optimized *B. Anthracis* DNA vaccine in different cationic lipid formulations. The results show higher neutralizing antibody titer. The example also teaches immunization of rabbit using codon optimized intramuscular administration of *B. Anthracis* DNA vaccine followed by aerosol administration of 50-250 LD_{50} equivalent of *B. Anthracis* (Ames strain) spores. The results show that all the codon optimized DNA vaccine formulations had comparable efficacy as compared to commercially available AVA vaccine. Examples 14-15 describe immunization of mice using formulation that is prepared by adding sterile plasmid DNA and sterile DMRIE: DOPE SUV liposome in a final molar ratio of 4:1 or 2:1 plasmid DNA to DMRIE and non human primate immunized by VR6292 formulation with Vaxfectin. The data shows enhanced anti PA IgG titer in different formulations (table 19-23). Example 16 shows long-term immune response in DNA immunized rabbit after anthrax spore challenge (pp 112, table 24).

Although instant application shows the potential role of codon optimized DNA vaccine against *B. Anthracis* infection, however, the specification does not provide any evidence that codon optimized polynucleotide could be delivered by any method using any route that would elicit a therapeutic effective level of sustained immune response that would confer immunity against infection over the full scope of the claims.

The specification contemplate using cationic lipids for delivering the DNA vaccine, however, The specification also describes treating anthrax in any subject having any form of anthrax by administering combination of co lipid. The specification contemplates using cationic lipids for delivering the DNA vaccine. The method disclosed in specification also contemplates using lipoplex-mediated delivery of DNA vaccine in the subject. Dass et al (Journal of Pharmacy and Pharmacology, 2002, 54, 593-601) describe various factors that influence lipoflex-mediated nucleic acid transfer *in vivo* that includes type of cationic lipid making up the vesicle, cationic to neutral lipid ratio, and type of neutral lipid in the vesicle (pp 594, col. 1, para 3). Dass et al conclude that in

spite of cationic lipid-DNA complex being the efficient way to deliver nucleic acid into cultured cells. However, it is noted that Dass et al emphasize that their *in vivo* efficacy of lipoflex mediated nucleic acid delivery has shown varying degree of success, primarily due to toxicity associated with these formulations (pp 598, col. 1, last para). It is noted that independent claims 215, 231, 245 and 262 require composition and a carrier comprising GAP-DMORIE and any co lipid. However, prior to instant invention, McCluskie teaches that the route of delivery of DNA vaccine influences immune responses in laboratory animals (McCluskie et al (1999) Mol. Med. 5:287-300; Abstract). Specifically, in one study McCluskie et al. observed lack of response to non-injected routes of administration of DNA based vaccines, such as oral routes, sub lingual, inhalation and vaginal wall due to variation in transfection efficiency (Abstract). Thus, it is not apparent as to how skilled artisan would carry over a method encompassing treating or preventing any subject infected with any form of anthrax infection by administering via any route a composition comprising DNA vaccine comprising formulations of GAP-DMORIE and any co lipid.

Furthermore, It is noted that, the specification does not teach whether disclosed DNA vaccine would be effective in treating or preventing anthrax infection by administering codon optimized DNA vaccine using either via any or local route in any vertebrate. The cited arts clearly indicate limitation of the DNA vaccine for the treatment or prevention of anthrax infection.

In conclusion, in view of breadth of the claims and absence of a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled for the claimed inventions commensurate with full scope. The specification and prior art do not teach a method of *in vivo* delivery of DNA vaccine such that it render any subject sufficiently to elicit a immune response for a sustained duration for the prevention or treatment of anthrax infection caused by any type or severity or route. An artisan of skill would have required undue experimentation to practice the method as claimed because the art of DNA vaccine and *in vivo* delivery and treatment of anthrax in general by

recombinant vaccine in vivo was unpredictable at the time of filing of this application as supported by the observations in the art record.

Response to the Arguments

Applicant arguments filed on 09/11/2006 have been fully considered but they are not fully persuasive. Applicant in their argument on page 28, paragraph 3 asserts that the claimed methods do not require any specific level of immune response other than to treat or prevent anthrax infection as defined in the specification. It is noted that Applicants direct to paragraph 57 and 116 for the specific definition of prevention or treatment. Applicant further argues that the claimed methods do not require an "optimal immune" response.

In response, it is emphasized that the intent of the cited references are not to show that a composition comprising a polynucleotide encoding a polypeptide would not elicit an immune response to the polypeptide, rather the intent is to demonstrate that only a optimal immune response would confer protection against anthrax infection. Contrary to applicants argument paragraph 57 and 116 do not explicitly define the term prevention. In fact, paragraph 116 only describes treatment of a "vertebrate refers to the use of one or more compositions of the present invention to prevent, cure, retard, or reduce the severity of anthrax disease symptoms in a vertebrate, and/or result in no worsening of anthrax disease over a specified period of time", while paragraph 57 states polypeptides:... of the present invention can be antigenic and immunogenic polypeptides related to *B. anthracis* polypeptides, which are used to prevent or treat, i.e., cure, ameliorate, lessen the severity of, or prevent or reduce contagion of infectious disease caused by *B. anthracis*". Thus, given the broadest reasonable interpretation claims 215-230, and 245-260 would also embrace complete protection against *B. anthracis* infection. However, prior art teaches that only a critical level of serum anti-PA antibodies confer immunity to both cutaneous and inhalation anthrax (Leppla et al., J Clin Invest. 2002,110(2): 141-4; supra). The specification does not provide any specific guidance regarding achieving optimal immune response against

anthrax infection to prevent infection. In fact applicant argue contrary to this and emphasize that claimed methods do not require any specific levels of immune response. Thus, it is apparent that contrary to applicants argument an artisan would have to adminster composition to the mammal in dosage sufficient to elicit sufficient immune response for long enough of time to confer any protection against anthrax infection.

Applicant also provides the references of Price et al to show that in spite of some variation in protective antigen among 26 strains *of B. anthracis*, there will instant amendments to 97% sequence identity to the polypeptide would allow for using PA from various strains of *B. anthracis* (seepage 29).

In response, Examiner agrees with the Applicants assertion that 97% sequence identity to the polypeptide would allow one skilled in the art for using PA from various strains of *B. anthracis*. However, in the instant case, it is noted that Applicant's contemplate delivering a composition that recites a term "wherein about" implying one more or one less codon in an optimized coding region for the polypeptide of SEQ ID NO: 4. Prior to instant invention, Nagata concluded that only optimal codon usage would elicit effective immune response. Nagata et al also suggested that translational efficiency of codon-substituted gene in mammalian cells does correlate but is not proportional to codon adaptation index (CAI) values of the genes in the mammals (Figure 2). Thus, it is clear that breadth of the claims also embraces other optimize sequences of PA would require further experimentation.

Applicant also argue that Examiner is requiring an unreasonable enablement standard and assert that a number of DNA vaccines are undergoing Phase I and Phase II human trial. Applicant uses the cited reference of Galloway et al to argue that it is possible to develop modalities that endure sufficient DNA uptake and effectively stimulate immune response (see page 31, paragrah1).

In response, it is again emphasized that issue at hand is not whether lipid formulation (as amended) comprising instant composition would elicit immune response, rather question is whether instant composition would elicit immune response to level sufficient to prevent anthrax infection. It is reiterated that instant claims embrace

a method to prevent anthrax infection by administering the composition to the vertebrate such that it elicit immune response to the polypeptide of the invention. Since, a minimal inflammation could also be considered as an immune response to the administration of a polypeptide but such an immune response or even sub optimal immune response would not be sufficient to practice the method as recited in the rejected claims.

Applicant in their argument on pages 31-33 asserts that in order to address Examiner's view of the enablement applicant would have to submit conclusive date from human clinical trial in order to adequately enable a method of treatment applicable to humans. Applicant also argues that it Is not within the province of the USPTO to require proof of efficacy in animal to grant a patent including claims to the therapeutic methods. Applicant asserts that only reasonable correlation must exit between the scope of the claim and scope of the enablement. Applicant argues that application describes various in vitro assays and describes various vaccine compositions in three different animal models. Applicant also cites the reference of post filing art by Hermanson et al (IDS, NPL4) to support the pre clinical safety studies in product selection (also see page 36 of the argument. Applicant also questions the reference of Leppla et al (IDS) and argues that exposing humans to anthrax will be unethical and is not required by FDA for anthrax vaccine (see pages 33 –34 of the argument)

In response, it appears that Applicant has analyzed the reference of Leppla solely to interpret that it would require human clinical trial to establish the efficacy of any vaccine to anthrax. Examiner had no intention to raise any toxicity or safety issue arising from any of the composition. The discussion is merely intended to address the breadth of independent claim 176 (now cancelled, presently amended as 215, 231, 245, 261) directed to a method of treating or preventing anthrax infection by composition disclosed in this application. The specification provides no specific definition of what is meant by the term "prevention". Given the broadest reasonable interpretation, it embraces complete protection against any form or type of infection. The reference of Leppla provides an analogy to describe the breadth of instant as well as previously rejected claims. It is noted that rejected claims only recite eliciting immune response to the composition of the invention but contemplates preventing or treating any vertebrate

that has infection or is at risk of developing infection of any magnitude (supra). As stated before in order to practice the entire breadth of the claim, an artisan would have to make a new invention in the field by optimizing codon of the PA in such a way that when delivered in appropriate carrier would result in appropriate levels of immune response against the composition for desired duration in order to prevent anthrax infection of any type. Since, specification does not provide what is included or excluded with the term prevention, applicants are only enabled to a method to reduce the severity of an anthrax infection consistent with the disclosure. Furthermore reference of Hermanson et al teach rabbits vaccinated with two or three injections of PA pDNA alone or in combination with LF pDNA showed no significant increase in anti-PA antibody titers post challenge (Fig. 2 *A*). It is noted that instant method of treating anthrax infection is different from one disclosed in cited art since instant claims do not require multiple administration of composition for priming the immune response. It is noted that the post filing art shows no significant increase in anti-PA antibody titers after exposure to pathogen. In the instant case, Examiner agrees that the disclosure as well as cited art provides enough corelationto show that administration of instant composition may result in reducing the severity of anthrax infection in a mammal that requires such a vaccination.

Applicant's arguments, with respect to references of Jones et al (page 36 of the argument) and Perrie et al have been fully considered but are moot in view of cancellation of rejected claims. It is also noted that Applicant argues that claims do not require an optimal immune response and asserts that example of the specification show that SEQ ID NO 8 and at least two type of formulation results in protective immunity against anthrax infection (see page 37, para. 4 of the arguments). In response, in the instant case, claims embrace a method to reduce severity of anthrax infection by delivering the composition set forth in claim 215. Applicant is arguing that claim do not require optimal immune response but at the same time also supports the enablement by referring to specification showing protective immune response against anthrax infection. It is emphasized that although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988

F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The method recited in independent claims are enabled only if instant method elicit optimal immune response against anthrax infection . Therefore, contrary to applicant arguments an artisan would have to perform undue experimentation to adminster composition to the mammal to elicit sufficient immune response for long enough of time to confer protection against anthrax infection as required by instant claims.

Withdrawn-Claim Rejections - 35 USC § 112

Claim 174 rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps is withdrawn in view of cancellation of claim 174.

Withdrawn-Claim Rejections - 35 USC § 102

Claims 139, 151 and 174 rejected under 35 U.S.C. 102(e) as being anticipated by Lee et al (US Patent Application no US 2004/0009945, dated 1/15/2004, effective filing date 7/10/1998) is withdrawn in view of cancellation of claims 139, 151 and 174.

Claim Rejections - 35 USC § 103

Claims 139 and 151 rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (US Patent Application no US 2004/0009945, dated 1/15/2004, effective filing date 7/10/1998) or Katritch et al (US Patent publication no. 20030235818, dated 12/25/2003, effective filing date 4/17/2002) or Collier et al (US Patent publication no. 20020039588, dated 4/4/2002, effective filing date 5/4/2000) and Nagata et al (Biochem Biophys Res Commun. 1999, 261(2): 445-51) is withdrawn in view of cancellation of claims 139, 151 and 174. Applicant's arguments with respect to instant claims have been considered but are moot in view of the new ground(s) of rejection.

New -Claim Rejections - Necessitated by amendment -35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 215-292 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (US Patent Application no US 2004/0009945, dated 1/15/2004, effective filing date 7/10/1998); Nagata et al (Biochem Biophys Res Commun. 1999, 261(2): 445-51) and Hartikka et al (2001, Vaccine 19:1911-1923).

Lee et al teach a method and composition for using the nontoxic protective antigen (PA) protein from *B. anthracis* in inducing an immune response that is protective against anthrax in subjects (abstract). It is noted that Lee et al disclose a SEQ ID NO: 6 (PA) that has 100% sequence similarity with claimed SEQ ID NO: 4 (see sequence search report). In addition Lee et al also teach SEQ ID NO: 5, that has ~97% sequence similarity with claimed variants set forth in SEQ ID NOs: 2, 4 and 6. It further disclosed that nucleic acid molecules could encode portions or fragments of the nucleotide sequences and variants of disclosed sequence (pp 2, para. 24 and 25). Lee et al emphasize that it would be routine for one skilled in the art to generate the degenerate variants, for instance, to optimize codon expression for a particular host (pp 2, para. 21, col. 2, lines 1-5). In addition, Lee et al contemplate using pharmaceutical carrier to deliver disclosed nucleic acid composition for eliciting immune response in a subject. Since the disclosed nucleic acid sequence is from *B. anthracis*, the codon usage pattern is considered related with the translation efficiency of the gene in different organisms. It is also noted that these compositions were generally directed towards enhancing immunity against *B. anthracis*.

The prior art differed from the claimed invention by not teaching delivering a composition comprising a combination of lipids comprising polynucleotide encoding

polypeptide of the invention that are codon optimized to enhance immune response in a subject using the *Homo sapiens* codon frequency table.

At the time of invention, Nagata et al teach that the codon optimization level of the genes correlate well with the translational efficiency in mammalian cells. This is concomitantly associated with the induction level of specific CTL response in the mouse using genes encoding major histocompatibility complex class I-restricted cytotoxic T-lymphocyte (CTL) epitopes, derived from an intracellular bacterium *Listeria monocytogenes* (see Table 1B and discussion). It is noted that the results of Nagata et al suggest that DNA immunization using the gene codon-optimized to mammals through the entire region is very effective (abstract). The teachings of Nagata et al suggest that the DNA sequence obtained by optimized codon usage of a host considerably increases both humoral and cellular immune responses (Figure 3 and discussion). Further, the teachings of Nagata et al indicate that synthetic human immunodeficiency virus type 1 gp120 sequence in which most wild-type codons were replaced with codons from highly expressed human genes (page 445, right column) is considerably increased in comparison to that of the respective wild-type sequence suggesting a direct correlation between expression levels of a protein obtained by codon optimization and the immune response. Although, Nagata generally teach that codon frequency table could be used to increases both humoral and cellular immune responses, but Nagata et al do not explicitly teach codon optimization for *B. anthracis*.

However, at the time the claimed invention was made, use of cationic lipid to deliver compositions to elicit immune response was routine in the art. Prior to instant invention, Hartikka et al teach variety of techniques to enhance humoral immune responses against pDNA-encoded antigen including co-injection of pDNA with neutral, anionic and/or cationic lipids. It is noted that Hartikka et al tested many carrier for improving the immune response and also disclose the optimized cationic carrier lipid:colipid formulation (1:1 molar mixture) of the cationic lipid (±)-*N*-(3-aminopropyl)-*N*,*N*-dimethyl-2,3-*bis*(*cis*-9-tetradecenyloxy)-1-propanaminium bromide, and a commercial colipid di-(3,7,11,15-tetramethyl-hexadecanoyl)phosphatidyl-ethanolamine (see page 1920. col. 1, para. 1). Hartikka et al also emphasize the importance of using

1:1 molar ratio of this composition in order to achieve optimal immune response. Although Hartikka et al do not explicitly teach a method to treat or prevent anthrax infection he generally embraced the idea that cationic lipids could potentially be used as adjuvant in genetic vaccination.

Accordingly, in view of the teachings of Lee, Nagata and Hartikka, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the composition of Lee by optimizing the codons with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification, as Lee had already disclosed that it would be routine for one skilled in the art to generate the degenerate variants, for instance, to optimize codon expression for a particular host (supra). Although Lee et al did not optimize the codon; he generally embraced potential of codon-optimized composition to reduce the severity of anthrax infection. In addition, Nagata also provided motivation of optimizing codon to improve immune response. Therefore, given that instant sequence and its potential to treat anthrax were known in prior art as per the teachings of Lee, it would have been obvious for an artisan to deliver the composition comprising codon optimized polynucleotide encoding polypeptide and a carrier such as one disclosed by Hartikka. The skilled artisan would have used the carrier disclosed by Hartikka particularly since prior art teach that this optimized cationic carrier formulation would have further enhanced the immune response.

One who would practiced the invention would have had reasonable expectation of success because a composition comprising a polynucleotide disclosed by Lee that is modified to alter the bacterial codon usage to human codon usage as taught by Nagata and delivered along with a carrier disclosed by Hartikka would have resulted in immune response to treat anthrax infection. An artisan of ordinary skills would have been motivated in using polynucleotide encoded by the sequence disclosed by Lee/ et al and further optimize for human codon usage to obtain highly efficient DNA because the prior art suggests that codon optimized DNA preparation is effective (Nagata et al discussion and abstract). One of ordinary skill in art would have been motivated to combine the teaching of Lee, Nagata and Hartikka because a composition comprising codon

optimized polynucleotide delivered along with a optimized cationic lipid would have been excellent candidate for DNA vaccine against anthrax.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Response to the Arguments

Applicant's arguments, see page 41-42, filed 9/11/2006, with respect to the rejection(s) of claim(s) 139, 151 and 174 under 35 USC 103(a) have been fully considered and are not fully persuasive. It is noted that applicants has cancelled these claims and have added new claims with new limitation. Therefore, instant response is directed to the extent it address the issues raised in previous office action. Applicant argues that prior arts do not suggest making the specific molecule modification necessary to achieve claimed invention. Applicants further argue that one can conceive a general process in advance for preparing an undefined compound does not mean that a claimed specific compound was precisely envisioned and therefore obvious. Applicant also indicate Nagata do not overcome this deficiency.

In response, it is clear from the cited reference that Lee taught a composition comprising SEQ ID NO: 4 and methods to treat anthrax infection (supra). In addition, Lee et al also suggested that a person skilled in the art could easily optimize the codon for better efficacy of the composition. Nagata taught the codon frequency table that could be used to increases both humoral and cellular immune responses. It would have required only routine optimization to reach to different codon optimized composition as recited in the rejected claims. Furthermore, these claims are broad and require one additional or one less codon as per the definition of "wherein about" as recited in the rejected claims. Thus, given the fact that instant claims are broad, it would be obvious for one skilled in the art to optimize codon for sequence disclosed by Lee to obtain a genus of codon optimized compositions including those recited in instant application for eliciting immune response to treat anthrax.

Conclusion

No Claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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